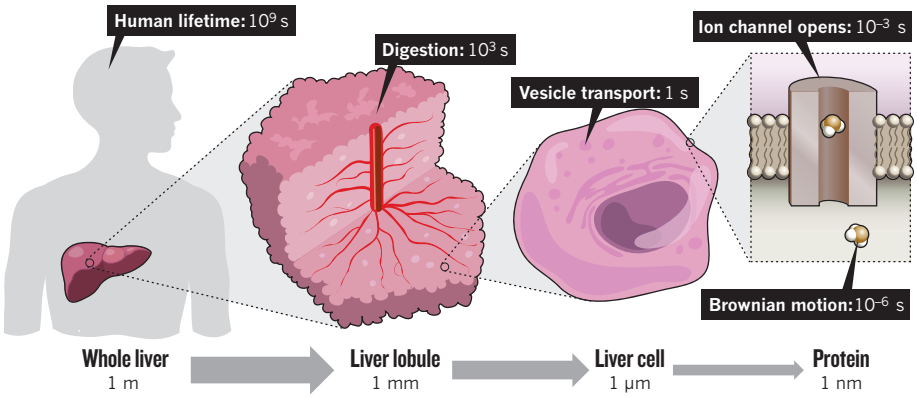
FROM MACRO TO NANO Modelling human liver function means integrating data at scales from the whole organ down to molecules, and decades to microseconds.



SYSTEMS BIOLOGY

Germans cook up liver project

Biologists join physicists in a bid to map the workings of the human organ at all scales.

BY ALISON ABBOTT

Systems biology — the holistic, interdisciplinary approach to modelling the processes of life — has set itself an ambitious new goal.

Launched in Dresden last week, the Virtual Liver Network is a German collaboration between biologists and theoretical physicists to model the functioning human liver. The work could help to develop more effective medicines, for example, because the metabolism of drugs in the liver has a profound impact on their efficacy and toxicity; or help in the understanding of liver disease. All foreign molecules are taken up into liver cells to be metabolized in preparation for excretion from the body.

Although some models of molecular pathways in liver cells can already predict how a drug may break down to become active or produce a toxic chemical, the biological consequences of this can only be predicted with a model of the liver's entire interacting system of cells and tissues. Similarly, a model of the entire liver will reveal much more about liver disease than a model of molecular interactions alone will.

The central challenge of the project lies in developing mathematical models that can unite data about processes that operate on vastly different temporal and spatial scales (see 'From macro to nano'). If successful, the network will integrate models of subcellular molecular signalling pathways with models of how a whole cell works, eventually building up a model of the entire organ that will be available to drug developers and other researchers.

Success will also depend on meeting an equally tough sociological challenge — getting 250 scientists in 69 research groups around Germany to work towards a common goal. "The network is very demanding and its principal investigators all have many different pressures to attend to," says Ursula Kummer, a modeller from the University of Heidelberg. "But we are all very excited about the challenge of multiscale modelling, and that's what motivates us."

The German federal research ministry has provided €43 million (US$57 million) to support the network for five years. It expands on the €36 million HepatoSys systems-biology programme, which between 2004 and 2009 worked towards modelling the hepatocyte, the most abundant cell in the liver.

The country's research community was hostile to HepatoSys at first, resenting the programme's top-down orchestration by the government's ministry of research. Many scientists also initially scorned the ministry's decision to use freshly dissected hepatocytes, rather than an off-the-shelf cultured liver cell line that would have been more convenient to use. It took years for HepatoSys scientists to develop protocols that ensured each batch of new cells would reach a standard quality in all research labs, but scientists have come round to the benefits. "We've found in fact that cell lines in culture don't behave much like real liver cells," says molecular biologist Ursula Klingmüller from the German Cancer Research Center in Heidelberg.

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And Marino Zerial, a director at the Max Planck Institute of Molecular Cell Biology and Genetics in Dresden, points out that hepatocytes offer "a great system for experimenters" because they naturally take up foreign molecules. Unlike most other cell types, they readily incorporate RNAi — RNA interference molecules, which target individual genes in cells for suppression or silencing.

HepatoSys involved 47 researchers, and some collaborating biologists and physicists formed intense bonds. Zerial and Yannis Kalaidzidis, his colleague at the institute, describe themselves as "almost inseparable".

Few papers have emerged from the six-year programme, but funders consider it a success. "We needed that amount of time to learn to speak each others' languages and to work to a common goal," says Gisela Miczka, who administers the Virtual Liver Network for the research ministry. "Plenty of papers from HepatoSys will start coming out in the next two years." With other colleagues in Dresden, Zerial and Kalaidzidis took five years to develop a model that describes how nutrients or signalling molecules are transported into the cell. They are only now preparing to submit a manuscript on the findings.

The Virtual Liver Network will continue to generate data and develop spatio-temporal models of biological events on the cellular scale, but will also try to generate a new theoretical framework for systems analysis at every scale of liver function. The multiscale modelling will rely on standard tools including differential equations and stochastic statistical methods, says Kalaidzidis, but it will also require more elaborate mathematics to bridge data sets at different scales. "There is no general recipe for moving between scales," he says, so the researchers must work out the essential features at each scale before applying them at the next level.

This is not the first attempt to model a human organ. Physiologists around the world have been working on a computational model of the heart for a few years, and this effort set the stage for a European Union programme on modelling different organs — the Virtual Physiological Human Network of Excellence, launched in 2008 — on multiple scales. "But we haven't yet really bridged the scales much," says Peter Hunter, director of the Bioengineering Institute at the University of Auckland in New Zealand, who was a major driving force behind the programme. The large size of the Virtual Liver Network and the basic, single-scale work that has already been done, means the liver effort "is well-placed to make breakthroughs". ■